BORTEZOMIB 21d

INDICATIONS

1- Relapsed or refractory multiple myeloma in patients who are at first relapse having received one prior line of therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances [NICE TA129]:

- the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) and
- the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above). [NICE TA129]

2- Induction treatment of adult patients with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation [NICE TA311]

3- Bortezomib is on the list of drugs routinely commissioned by NHSE (baseline commissioning) for the following indications:

- 1st line treatment of multiple myeloma in patients who are not NICE eligible for bortezomib due to presentation with:
  a) Severe renal failure contraindicating standard therapy (< 30 ml/min) or on haemodialysis
  b) Multisystem amyloidosis (on amyloid centre review)
- 1st line treatment of multiple myeloma in patients for whom transplant is considered unsuitable

4- Relapsed or refractory multiple myeloma in patients who are at second or more relapse and who have not received prior bortezomib based therapy.
Funding from the Cancer Drugs Fund is required. Requires **Blueteq** application

Note: The 21d regimen was the original standard of care and is particularly useful where a rapid response is required. For other patients, weekly dosing via one of the other bortezomib protocols is in general preferred to reduce toxicity. A protocol for a 35d regimen is also approved for patients with lower performance status or in whom co-morbidity precludes twice weekly dosing. Unless there is a contraindication to steroids, the use of Dexamethasone, given on the day of and the day after each dose of bortezomib, is recommended to improve response rates.

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - Baseline random blood glucose level
   - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
   - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
   - Serum free light chain assay (Freelite)
   - Hevylite analysis (if paraprotein level difficult to quantify)
   - β_2 microglobulin
   - LDH
   - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to Wessex Regional Genetics Laboratory (address below)
   - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
   - Group and save
   - Imaging as per NICE/network guidance and clinical presentation
   - Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospital
Salisbury
Wiltshire
SP2 8BJ

Additional Investigations
   - Plasma viscosity if hyperviscosity suspected.
   - If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology
2. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.
3. Fertility - all patients should be offered fertility advice, as appropriate.
4. Hydration - fluid intake of at least 3 litres /day should be attempted.
5. Document patient's height and weight, dose on actual body weight.
6. Document patient's performance status.
7. Treatment must be agreed at the relevant MDT

REGIMEN SPECIFIC PRE ASSESMENT

1. Evaluate for presence of neuropathy. This is usually done by clinical assessment although nerve conduction studies may be useful in occasional patients to document the extent of neurological damage prior to treatment with bortezomib. Baseline clinical assessment must be documented in the notes before the first dose of bortezomib is prescribed.

2. Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1.

DRUG REGIMEN

Bortezomib	1.3 mg/m^2 given as SC bolus	Days 1, 4, 8 and 11 on a 21 day cycle.
	WITH	
Dexamethasone	20 mg PO once daily	Day of and day after each bortezomib dose. This will usually be days 1, 2, 4, 5, 8, 9, 11 & 12.

At least 72 hours should elapse between consecutive doses of bortezomib.

CYCLE FREQUENCY

Repeat every 21 days until signs of disease progression or unacceptable toxicity for up to 8 cycles in total.

Allowable number of doses is as follows

- 24 doses for transplant eligible patients (first line of treatment)
- 51 doses for transplant ineligible (first line of treatment) patients
- 32 doses at first relapse

It is recommended that patients with a maximal response receive 2 additional cycles of treatment beyond confirmation of this status to a maximum of 8 treatment cycles. If there is no response after 2 cycles, the addition of Cyclophosphamide 500mg weekly to the Bortezomib and Dexamethasone may be clinically appropriate (alternate regimen, CyBorDex).

The NICE authorisation states that if patients have failed to reach at least a 50% reduction in paraprotein after 4 cycles, there will be no funding for any further courses and the drug must be stopped. In those circumstances the manufacturers will refund the cost of the 4 cycles via the established rebate scheme. Patients should have formal assessment of response documented in the notes prior to proceeding to cycle #5. In patients with non-secretory myeloma, this may require a repeat bone marrow aspirate / trephine.

DOSE MODIFICATIONS

Haematological Toxicity:
BORTEZOMIB:
Thrombocytopenia due to bortezomib is transient and very rarely causes significant bleeding. If baseline platelet count is > 70, then the risk of severe thrombocytopenia is very low

In such patients, FBC should be checked only at the start of the cycle and does not need to be repeated before each dose.

In patients with platelet count < 70 at the start of each cycle, the FBC should be checked before each dose, the drug should be withheld until FBC is through, and the dose omitted if platelets are < 25 unless thrombocytopenia is thought to be mainly due to marrow infiltration by myeloma. In those circumstances, consider proceeding with treatment with platelet transfusion support.

Otherwise, withhold at G3 non-haem (excluding neuropathy, see below) or G4 haem toxicities. Once resolved, re-initiate at 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinue unless benefit outweighs risk.

Peripheral neuropathy

Patients with pre-existing severe neuropathy may be treated with Bortezomib only after careful risk/benefit assessment.

Grading of neuropathy	Dose modification
G1 with no pain or loss of function	None
G1 with pain or G2	Reduce to 1.0 mg/m^2 or change treatment schedule to 1.3 mg/m^2 once per week if currently is twice per week
G2 with pain or G3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves, re-initiate treatment at 0.7 mg/m^2 once per week.
G4 and/or severe autonomic neuropathy	Discontinue

Hepatic/Renal Impairment

Renal	Hepatic
For dialysis patients, bortezomib should be given after dialysis No dose reduction necessary	Bil 1.0-1.5 x ULN: no dose reduction required Bili > 1.5 x ULN: reeduce to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.

INVESTIGATIONS (at the beginning of each cycle unless otherwise noted)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC (in patients with thrombocytopenia, consider checking FBC prior to each dose of bortezomib)

- U&E, LFTs, Ca^{++} – every 3 weeks
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle of bortezomib.
- Blood pressure (consider checking for postural drop if symptomatic)
- Ig's, paraprotein, Freelite assay.
- Consider repeat BM aspirate and trephine after 3 cycles in non-secretory myeloma, and check result prior to starting cycle 5.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

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CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and for 3 months after stopping bortezomib
- Prophylactic fluconazole 50mg OD
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Proton Pump Inhibitor or H2 antagonists at clinician's discretion.
- Bone protection as per NSSG Bone Protection protocol MM.3

Patients on bortezomib should be closely monitored if on CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). The concomitant use of bortezomib with strong CYP3A4-inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, and St John's wort) is not recommended as efficacy may be reduced.

Extravasation risk: bortezomib-irritant

Emetic Risk
Low emetic risk.

ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS

- **Peripheral neuropathy**: Patients should be advised to report pain hypersensitivity prickling, numbness and paraesthesia. If these occur see above dose reductions and consider use of Amitriptyline, Gabapentin and Pain Team referral. Neuropathy assessment tools are available in DTU. Caution in patients with existing peripheral neuropathy.
- **Dizziness and orthostatic hypotension:** Patients should be advised that Bortezomib may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position. Caution in patients with history of syncope, receiving medications associated with hypotension and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells. Patients who experience dizziness or low blood pressure may benefit from 500ml intravenous 0.9% sodium chloride with each dose of bortezomib.

- **Gastrointestinal**: Nausea, diarrhoea, vomiting and constipation are very common and ileus has been reported.
- Herpes zoster virus reactivation, progressive multifocal leukoencephalopathy (PML).

REFERENCES

1. Richardson PG, Sonneveld P, Schuster MW et al. for the Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005 Jun 16;352(24):2487-98.
2. Ailawadhi S, Mashtare TL, Coignet MV et al. Renal dysfunction does not affect clinical response in multiple myeloma (MM) patients treated with Bortezomib-based regimens. Blood. 2007; 110:Abstract 1477.
3. Richardson P, Mitsiades C, Schlossman R et al. The treatment of relapsed and refractory multiple myeloma. Hematology Am Soc Hematol Educ Program. 2007;2007:317-23.
4. Kropff M, Bisping G, Liebisch P, et al. Bortezomib in combination with high-dose dexamethasone and continuous low-dose oral cyclophosphamide for relapsed multiple myeloma. Blood. 2005; 106:Abstract 2549.
5. Lonial S, Waller EK, Richardson PG, Jagannath S, Orlowski RZ, Giver CR, Jaye DL, Francis D, Giusti S, Torre C, Barlogie B, Berenson JR, Singhal S, Schenkein DP, Esseltine DL, Anderson J, Xiao H, Heffner LT, Anderson KC; SUMMIT/CREST Investigators. Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed, refractory multiple myeloma. Blood. 2005 Dec 1;106(12):3777-84.
6. Heher EC, Goes NB, Spitzer TR, Raje NS, Humphreys BD, Anderson KC, Richardson PG. Kidney disease associated with plasma cell dyscrasias. Blood. 2010 Sep 2;116(9):1397-404.
7. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol. 2011 May;12(5):431-40.
8. Merz M, Salwender H, Haenel M, Mai EK, Bertsch U, Kunz C, Hielscher T, Blau IW, Scheid C, Hose D, Seckinger A, Jauch A, Hillengass J, Raab MS, Schurich B, Munder M, Schmidt-Wolf IG, Gerecke C, Lindemann HW, Zeis M, Weisel K, Duerig J, Goldschmidt H. Subcutaneous versus intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: Interim analysis from the prospective GMMG-MM5 trial. Haematologica. 2015 Apr 3. pii: haematol.2015.124347.
9. National institute of Health and Clinical Excellence. 2007. Internet. Bortezomib monotherapy for relapsed multiple myeloma (TA129). Online. Available at: https://www.nice.org.uk/guidance/ta129/chapter/1-guidance
10. National institute of Health and Clinical Excellence. 2014. Internet. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311). Online. Available at: https://www.nice.org.uk/guidance/TA311/chapter/1-guidance
11. Velcade ® Borrezomib eMC UK Summary of Product Characteristics, Janssen, February 2019

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, adverse effects and pre assessment section	May 2016	1.3	May 2018
Dr Jaimal Kothari Consultant	Regimen specific pre assessment included	May 2016	1.3	May 2018
Manuela Sultanova Service Coordinator	Formatting, standardisation of some sections e.g pre-assessment, wording about dizziness in Adverse effects	July 2017	1.4	May 2018
Network Protocol Review	Funding. Standardisation of assessment, renal modifications, investigations supports, adverse events.	June 2018	1.5	June 2018
Myeloma Protocol Review 2019	Addition of allowable number of doses per treatment line, dose modifications, clarification of dosing in hepatic impairment, concurrent medication, extravasation risk, update of references	June 2019	1.6	June 2020
Quality manager	Nursing care plan added	April 2021	1.7	June 2020

Nursing Care Plan: Bortezomib (Velcade) 21 day

Indication: Relapsed/refractory Myeloma.

Frequency: Every 21 days for up to 8 cycles (used where a rapid response to treatment is required).

Alopecia: No

BORTEZOMIB (VELCADE): Proteasome inhibitor.

Administered subcutaneously **on days 1, 4, 8 and 11**. Minimum of 72 hours required between doses.

Emetic risk: low

Classification of extravasation: Irritant

Side effects: tachycardia, diarrhoea, constipation, anorexia, nausea/vomiting, thrombocytopenia, neutropenia, peripheral neuropathy (sensory and motor), headache, rash, fatigue, postural hypotension, dizziness, shingles, inflammation at injection site, infections, bone marrow depression.

DEXAMETHASONE: corticosteroid tablets

Administered orally on the day of each Bortezomib dose and the day after. Taken with or after food preferably at breakfast

Side effects: restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression.

Regime Specific Considerations

- Lying and standing blood pressure to be recorded pre cycle 1, advise patients that velcade can cause orthostatic hypotension and counsel them to sit upright for a moment before standing from a sitting/lying position.
- Advise patients to maintain a fluid intake of 2-3 litres and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.
- Assess for presence of peripheral neuropathy before starting treatment and **prior to the start of each cycle.**

Bloods are required at the start of each cycle. Patients with unstable blood counts (specifically low platelets, see protocol) may require more frequent monitoring.